

**In the claims:**

Please cancel claims 2 and 3.

**REMARKS**

In the Office Action dated as mailed January 16, 1007, the Examiner rejects claims 1,4-9, 65, 67-80 and 82 under 35 USC § 103 as being unpatentable over a combination of Wolicki (US2004/0101582) in view of Williams et al. (U.S. 2003/0082214) or Murdock at al (6,572,88). The Applicant respectfully submits that the Examiner cannot sustain a prima facie case of obviousness by reliance on the cited references. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combined reference teachings. Second , there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicant respectfully submits that none of the three factors are met by the cited combination.

**A. There is no Suggestion to Combine the Reference Teachings**

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir 1990). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claims invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.

Cir. 1983), cert. denied, 469 U.S. 851 (1984). It is improper to combine references where the reference teach away from their combination. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). A prior art reference that "teaches away" from the claim invention is a significant factor to be considered in determining obviousness. MPEP §2145 (X)(D)(1).

Applicant's invention, as amended, is directed to a topical composition comprising amitriptyline, clonidine, ketamine and an anti-inflammatory in a base. The Examiner states that Williams teaches using non-steroidal anti-inflammatory analgesics. In fact, Williams teaches directly away from the present invention stating:

Examples of local anesthetics suitable for use with the invention include sodium-channel blockers. Sodium-channel blockers, such as lidocaine prevent the generation and conduction of nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na<sup>+</sup>. Examples of sodium-channel blockers include, but are not limited to, ambucaine, amolanone, amylcaine, benoxinate, benzocaine, betoxycaaine, biphenamine, bupivacaine, butacaine, butamben, butanilicaine, butethamine, butoxycaaine, carticaine, chloroprocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dyclonine, ecogonidine, ecogonine, euprocin, fenalcomine, formocaine, hexylcaine, hydroxyteteracaine, isobutyl p-aminobenzoate, leucinocaine, levoadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octacaine, orthocaine, oxethazaine, parenthoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propiprocaine, propoxycaine, pseudococaine, pyrrocaaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, or pharmaceutically-acceptable salts thereof, or mixtures thereof. Preferred sodium-channel blockers, include lidocaine, procaine, bupivacaine, prilocaine, mepivacaine, etidocaine, ropivacaine, dibucaine, and pharmaceutically-acceptable salts thereof and mixtures thereof. The most preferred local anesthetic is lidocaine and pharmaceutically acceptable salts thereof.

The Williams reference goes on to state "Other agents with local-anesthetic properties include analgesics, such as non-steroidal anti-inflammatories ("NSAIDs")". The Williams reference teaches directly away from the present invention providing a list of "local anesthetics suitable for use with the invention" and then goes on to state there are "other agents", which no suggestion or motivation to use such agents in relation to the Williams composition and certainly no suggestion or motivation to combine the references with the Wolicki reference.

Wolicki teaches away from the present invention and states, "The NSAIDs, for example, when taken orally cause gastric distress—including ulcers. The other three classes share other common side effects, including drowsiness, dizziness, disorientation, and gastrointestinal upset to name but a few." Paragraph [011].

Murdock provides "A transdermal composition for the relief of pain in a subject comprising lamotrigine, doxepin and a muscle relaxant selected from the group consisting of guaifenesin chlorzoxazone dantrolene sodium, metaxalone, carisoprodol, and combinations thereof, in lecithin organogel, wherein said pain relief obtainable from the combination of lamotrigine, doxepin and muscle relaxant exceeds the degree of pain relief obtainable from doxepin alone". Murdock provides, "another embodiment of the invention features a transdermal composition which includes an amine-containing compound as described herein and an anti-inflammatory compound such as a nonsteroidal anti-inflammatory compound, e.g., celecoxib, etodolac, mefanamic acid, nabumetone, salsalate, naproxen, vioxx.RTM., and combinations thereof. Such a composition can further include an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant such as guaifenesin." There is no suggestion or motivation to combined the Murdock reference with the Williams or Wolicki reference.

**B. There is no reasonable expectation of success**

1. Wolicki teaches away from the present invention and states, "The NSAIDs, for example, when taken orally cause gastric distress--including ulcers. The other three classes share other common side effects, including drowsiness, dizziness, disorientation, and gastrointestinal upset to name but a few." Paragraph [011]

2. Williams states (column 35, lines 4-8) "Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and prioxicam, the effect appears to be relatively weak compared to the effect provided by doxepin."

3. Murdock provides "A transdermal composition for the relief of pain in a subject comprising lamotrigine, doxepin and a muscle relaxant selected from the group consisting of guaifenesin chlorzoxazone dantrolene sodium, metaxalone, carisoprodol, and combinations thereof, in lecithin organogel, wherein said pain relief obtainable from the combination of lamotrigine, doxepin and muscle relaxant exceeds the degree of pain relief obtainable from doxepin alone".

**C. Not all limitations are found in the References**

1. Wolicki does not disclose anti-inflammatory and states that they may cause drowsiness, dizziness, disorientation, and gastrointestinal upset.

2. Williams does not provide any reference to anti-inflammatory, amitriptyline, clonidine.

3. The only relevance of the Murdock reference is that it provides an anti-inflammatory. However, there is no suggestion of any of the other limitations as in the Applicants application.

**D. Conclusion**

The cited references do not provide: (1) any motivation to combine the three references and in fact teach away from the present invention; (2) a likelihood that the combination would be successful; or (3) a teaching or disclosure of all the claimed limitations. Accordingly, Applicant respectfully submits that a *prima facie* case of obviousness cannot be maintained and that the rejection should be withdrawn.

In view of the above remarks, Applicant respectfully believes that all pending claims are in a condition for allowance, and prompt and favorable action on all claims are respectfully requested.

In the event the examiner wishes to discuss any aspect of this response, please contact the attorney at the telephone number identified below.

Respectfully submitted,

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